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Applicant(s): RHONE POULENC SA ;

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ABSTRACT:

Novel urea and thiourea derivatives of Formula I wherein X is oxygen or sulphur, A is a straight or branched alkylene group having 1-4 carbon atoms, the groups -NH- and -CO-attached to a common benzene nucleus are in meta or para position in relation to one another, R and R1 are hydrogen or methyl, and the groupings -NH- and -CH3 attached to a common benzene nucleus are in ortho position in relation to one another, and acid addition salts thereof, are prepared by reacting two moles of an amino-amidine of Formula II or an acid addition salt thereof, with one mole of carbonyldiimidazole or thiocarbonyldiimidazole, with or without an inert and anhydrous organic solvent at a temperature between ambient and 120 DEG C., or by reacting one mole of a 1,3-bis-(3-chlorocarbonylphenyl)-urea or -thiourea with two moles of an aminoamidine of formula and, in each case, optionally converting the product obtained into an acid addition salt. The starting materials of Formula II may be prepared by the series of reactions shown in the following reaction scheme: The bis(3-chlorocarbonylphenyl)-ureas or thioureas may be prepared by treating the corresponding diacid obtained by reacting amino-benzoic acid with urea, with thionyl chloride. The amidines of Formula II may also be prepared by treating a (nitrobenzamido)-benzoic acid with thionyl chloride, reacting the acid chloride with an aminonitrile, treating the [(nitrobenzamido)-benzamido]-nitrile with dry gaseous hydrogen chloride in chloroform/ethanol, isolating the imino-ether hydrochloride and treating this with anhydrous ammonia at 0 DEG C. to give the [(nitrobenzamido)benzamido]-amidine which is then hydrogenated. Therapeutic compositions having anti-viral and hepatoprotective activity, which may be administered parenterally, or orally, contain as active ingredient at least one compound of Formula I above or a non-toxic acid addition salt thereof.

PATENT SPECIFICATION

NO DRAWINGS

1.110.099

1.110.099

Inventor: MARC JULIA

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Int. Cl.:—C 07 c 127/16

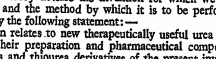
COMPLETE SPECIFICATION

Urea and Thiourea Derivatives

We, RHONE-POULENC S.A., a French Body Corporate of 22 Avenue Montaigne, Paris, France, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new therapeutically useful urea and thiourea derivatives, to processes for their preparation and pharmaceutical compositions containing them.

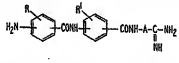
The new urea and thiourea derivatives of the present invention are compounds of the general formula:



I

wherein X represents an oxygen or sulphur atom, A represents a straight or branched alkylene group having from 1 to 4 carbon atoms, the groupings NH and CO attached to a common benzene nucleus are in *meta*- or *para*-position in relation to one another, each of the symbols R and R', which are identical or different, represents a hydrogen atom or a methyl group, and the groupings NH and CH_2 attached to a common benzene nucleus are in *ortho*-position in relation to one another, and acid addition salts thereof.

According to a feature of the invention, the aforesaid urea and thiourea derivatives are prepared by reacting two moles of an amino-amidine of the general formula:

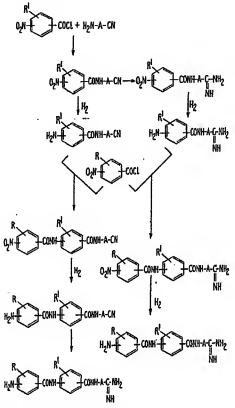


II

wherein the symbols are as hereinbefore defined and in which the position of the substituents is that previously indicated, or an acid addition salt thereof, with one mole of carbonyldiimidazole or thiocarbonyldiimidazole with or without an inert and anhydrous organic solvent at a temperature between ambient temperature (20°C.) and 120°C. according to the method of H. A. Staab, Ann, *609*, 75 (1957), and optionally converting the product obtained into an acid addition salt. Preferably, the reaction is effected with an amino-amidine hydrochloride in solution in anhydrous dimethylformamide at a temperature between ambient temperature (20°C.) and 85°C.

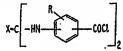
[*Price 4s. 6d.*]

The amidines of the formula II may be prepared by application of known methods e.g. in accordance with any one of the series of reactions depicted in the following scheme: —



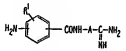
wherein the various symbols are as hereinbefore defined.

According to another feature of the invention, the compounds of formula I are prepared by reacting one mole of a dichloride of the formula:



III

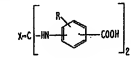
wherein X and R are as hereinbefore defined, with two moles of an amino-amidine of the general formula:



IV

wherein R' is as hereinbefore defined, and optionally converting the product obtained into an acid addition salt. The reaction may be effected by heating the reactants in an inert organic solvent such as dimethylformamide in the presence of pyridine.

The dichlorides of formula III may be prepared by the action of thionyl chloride on the diacid of the formula:



V

wherein X and R are as hereinbefore defined, the reaction being carried out in dimethylformamide.

The urea and thiourea derivatives of formula I may be converted by methods known *per se* into acid addition salts. Such salts may be obtained by the action of acids on the urea or thiourea derivatives in appropriate solvents. As organic solvents there may be used, for example, alcohols, ethers or ketones; water may advantageously be used as an inorganic solvent. The acid addition salt which is formed is precipitated, if necessary after concentration of the solution, and is separated by filtration or decantation.

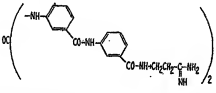
The compounds of formula I and their acid addition salts possess interesting chemotherapeutic properties. They are useful as antiviral agents, more particularly against the influenza virus and viral hepatitis, and also as hepatoprotective agents. Preferred compounds are those in which A represents ethylene and, in particular, 1,3 - bis{3 - [3 - (2 - amidinoethyl)carbamoylphenyl]carbamoylphenyl}urea, 1,3-bis{3 - [3 - (2 - amidinoethyl)carbamoyl - 6 - methylphenyl]carbamoylphenyl}urea, 1,3 - bis{3 - [3 - (2 - amidinoethyl)carbamoylphenyl]carbamoyl - 6 - methylphenyl}-urea and 1,3 - bis{3 - [3 - (2 - amidinoethyl)carbamoyl - 6 - methylphenyl]-carbamoyl - 6 - methylphenyl}urea, and acid addition salts thereof.

For therapeutic purposes, the urea and thiourea derivatives of formula I are employed as such or in the form of non-toxic acid addition salts, i.e. salts containing anions which are relatively innocuous to the animal organism in therapeutic doses of the salts (such as hydrochlorides and other hydrohalides, phosphates, nitrates, sulphates, acetates, propionates, oxalates, succinates, benzoates, picrates, fumarates, maleates, citrates, tartrates, salicylates, methylene-bis-β-hydroxynaphthoates, gentisates, methanesulphonates, ethanedisulphonates, benzenesulphonates, and toluene *p*-sulphonates) so that the beneficial physiological properties inherent in the bases are not vitiated by side effects ascribable to the anions.

The following Examples, in which the percentage yields mentioned are in relation to the theoretical yield, illustrate the invention.

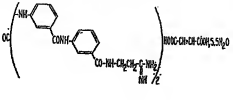
EXAMPLE I

A suspension of 3-[3-(3-aminobenzamido)benzamido]propionamidine hydrochloride (3.6 g., 0.01 mol.) in anhydrous redistilled dimethylformamide (15 cc.) is heated to 70°C. and carbonyldiimidazole (1 g., 0.005 mol.) is added. The mixture is heated for half an hour at 80°C. and then allowed to stand for twelve hours. The dimethylformamide is evaporated *in vacuo* and the oily residue is washed several times with acetone and then dissolved in water (25 cc.). The aqueous solution is agitated for 2 hours with a suspension of an ion exchange resin having carboxylic groups (10 g.) in water (100 cc.) to absorb the unreacted amine, and then it is filtered and the filtrate concentrated *in vacuo*. There is thus obtained a light brown oily residue (1.6 g., i.e. a yield of 45%) which is the dihydrochloride of the compound of the formula:



which is identifiable by its crystalline fumarate, m.p. 212—215°C., obtained in the following manner:

To the oily dihydrochloride (1.6 cc.) in solution in water (20 cc.) is added sodium fumarate (0.5 g.) and the precipitate is filtered off and recrystallised from water. There is thus obtained the product (1.9 g.) of the formula:



3 - [3 - (3 - Aminobenzamido)benzamido]propionamidine hydrochloride employed as starting material is prepared by hydrogenating under ambient pressure and at ambient temperature and in the presence of Raney nickel (1 g.) a suspension of 3-[3-(3-nitrobenzamido)benzamido]propionamidine hydrochloride (5 g., 0.00125 mol.) in absolute ethanol (250 cc.) (absorption 850 cc. of hydrogen). The catalyst is filtered off and the filtrate is concentrated *in vacuo*. There is thus obtained 3-[3-(3-aminobenzamido)benzamido]propionamidine hydrochloride (3.8 g., yield 84%), m.p. 158—160°C. (the dihydrochloride melts at 218—220°C.).

3-[3-(3-Nitrobenzamido)benzamido]propionamidine hydrochloride is prepared by the method of Goldberg and Kelly, J. Chem. Soc., 1372 (1947). A suspension of 3-[3-(3-nitrobenzamido)benzamido]propionitrile (12 g., 0.04 mol.) in chloroform (60 cc.) and absolute ethanol (4 cc.) is saturated at 0°C. with dry gaseous hydrogen chloride. After standing for five days, the iminoether hydrochloride thus formed is precipitated with anhydrous diethyl ether (250 cc.). The precipitate is filtered off and suspended in absolute ethanol (100 cc.) and the suspension is saturated at 0°C. with anhydrous ammonia. The reaction mixture is allowed to stand overnight and the ammonia is driven off *in vacuo*. There is obtained 3-[3-(3-nitrobenzamido)benzamido]propionamidine hydrochloride (10.8 g., yield 82%), m.p. 142—145°C. after recrystallization from a mixture of ethanol and water.

For preparing 3-[3-(3-nitrobenzamido)benzamido]propionitrile, 3-(3-nitrobenzamido)benzoyl chloride (110 g., 0.36 mol.) is gradually added to a cold solution of 3-aminopropionitrile (25 g., 0.36 mol.) in anhydrous pyridine (420 cc.). The mixture is poured very quickly into iced water and the precipitate is filtered off. There is thus obtained 3 - [3 - (3 - nitrobenzamido)benzamido] propionitrile, (106 g., yield 93%), m.p. 180°C.

3-(3-Nitrobenzamido)benzoic acid, m.p. 298—300°C., may be prepared by the method of Bredereck and Von Schuh, Ber. *81* 218, (1948), in a yield of 95%. On treatment with an excess of thionyl chloride heated under reflux, it gives in a yield of 89% 3-(3-nitrobenzamido)benzoyl chloride, m.p. 155—156°C.

Example II

A suspension of 3-[4-(4-aminobenzamido)benzamido]propionamidine hydrochloride (3.6 g.) in dimethylformamide (15 cc.) is heated to 80°C., and carbonyldiimidazole (1 g.) is then added. The reaction mixture is heated at 70—80°C. for 30 minutes, filtered, and water (50 cc.) is added. The precipitate obtained is separated and washed with N hydrochloric acid, then with water and finally with ethanol. The gelatinous precipitate obtained is dissolved in hexamethylphosphotriamide and then again precipitated by adding ethanol. After filtering and washing with ethanol, there is obtained 1,3 - bis{4 - [4 - (2 - amidinoethyl)carbamoylphenyl]carbamoylphenyl}-urea dihydrochloride (2 g.), m.p. 320—325°C.

The initial 3-[4-(4-aminobenzamido)benzamido]propionamidine hydrochloride is prepared by hydrogenating at ambient pressure and temperature in the presence of Raney nickel)1 g.) a suspension of 3-[4-(4-nitrobenzamido)benzamido]propionamidine hydrochloride (3 g.) in ethanol (50 cc.) (absorption 515 cc. of hydrogen). After filtering and washing a number of times with water, the filtrate is concentrated to dryness *in vacuo* and recrystallised from ethanol. There is obtained 3-[4-(4-aminobenzamido)-benzamido]propionamidine hydrochloride (2.3 g.), m.p. 262—264°C. (the dihydrochloride melts at 248—250°C.).

3-[4-(4-Nitrobenzamido)benzamido]propionamidine hydrochloride is prepared by saturating a suspension of 3-[4-(4-nitrobenzamido)benzamido]propionitrile (12 g.) in chloroform (100 cc.) and ethanol (10 cc.) at 0°C. with dry gaseous hydrogen chloride. After standing for 10 days at ambient temperature, the iminoether hydrochloride formed is precipitated with anhydrous diethyl ether (300 cc.), filtered off and washed with anhydrous diethyl ether. It is then dissolved in ethanol (300 cc.) and the solution obtained is saturated with anhydrous ammonia at 0°C. The reaction mixture is allowed to stand for 2 days, the ammonia is eliminated *in vacuo* and the solution acidified to a pH of 2—3 with hydrochloric acid in solution in ethanol. After recrystallisation from water, 3-[4-(4-nitrobenzamido)benzamido]propionamidine hydrochloride (12.5 g.), m.p. 270—272°C., is obtained.

3-[4-(4-Nitrobenzamido)benzamido]propionitrile is prepared by condensing 4-(4-nitrobenzamido)benzoyl chloride (110 g.) with 3-aminopropionitrile (25 g.) in anhydrous pyridine (450 cc.) between 5° and 10°C. The reaction mixture is poured into iced water (1 litre) and the precipitate obtained is filtered off, washed with an aqueous sodium bicarbonate solution, N hydrochloric acid and finally with water, and then

recrystallised from a mixture of dimethylformamide and ethanol. There is thus obtained 3-[4-(4-nitrobenzamido)benzamido]propionitrile (105 g.), m.p. 243°C.

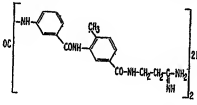
4-(4-Nitrobenzamido)benzoyl chloride (m.p. 168—172°C.) is prepared by the action of thionyl choride on 4-(4-nitrobenzamido)benzoic acid, which is itself prepared in accordance with Bredereck and von Schub, Ber. *81*, 218 (1948).

Example III

Thiocarbonyldiimidazole (2.67 g.) and 3-[4-(4-aminobenzamido)benzamido]-propionamidine hydrochloride (10.86 g.) are dissolved in dimethylformamide (60 cc.) The reaction mixture is allowed to stand for 12 hours and the dimethylformamide is then evaporated *in vacuo*. Acetone is added to the residue thus obtained and is decanted with trituration. The residue is dissolved in water and the solution obtained is then filtered and concentrated. Acetone is added and the precipitate obtained, after filtration, is washed with acetone and ethanol to give 1,3-bis{4-[4-(2-amidinoethyl)carbamoyl-phenyl]carbamoylphenyl}thiourea dihydrochloride (7 g.), m.p. 267°C.

Example IV

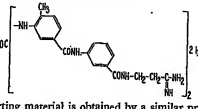
A suspension of 3-[3-(3-aminobenzamido)-4-methylbenzamido]propionamidine hydrochloride (3.75 g., 0.01 mol.) in dimethylformamide (15 cc.) is heated to about 70°C., and carbonyldiimidazole (1.3 g.) is then added. The reaction mixture is heated at 70°C. for 30 minutes, then left overnight and the product precipitated by the addition of water (50 cc.). The precipitate obtained is filtered off, washed, redissolved in dimethylformamide (10 cc.) and reprecipitated by the addition of acetone. This redissolving and reprecipitating treatment is repeated 3 times, the last precipitation being carried out, not with acetone, but with water. After drying, there is obtained a product (1.2 g.) melting at 170—175°C. and conforming to the following formula:



The initial 3-[3-(3-aminobenzamido)-4-methylbenzamido]propionamidine hydrochloride, m.p. 181—183°C., is prepared by application of a series of reactions known *per se* from 3-(3-nitro-4-methylbenzamido)propionitrile, m.p. 141°C., which is converted into 3-(3-nitro-4-methylbenzamido)propionamidine hydrochloride, m.p. 228—230°C., which is reduced by hydrogen in the presence of Raney nickel to form 3-(3-amino-4-methylbenzamido)propionamidine hydrochloride, m.p. 225—228°C. The amino compound is condensed with *m*-nitrobenzoyl chloride to form 3-[3-(3-nitrobenzamido)-4-methylbenzamido]propionamidine hydrochloride, m.p. 158°C., which is reduced by hydrogen in the presence of Raney nickel.

Example V

By proceeding as indicated in the preceding Example and starting with 3-[3-(3-amino-4-methylbenzamido)benzamido]propionamidine hydrochloride (3.75 g., 0.01 mol.), m.p. 213—214°C., and carbonyldiimidazole (1.3 g.) there is obtained a product (1.5 g.) melting at 220—224°C., of the formula:



The amidino starting material is obtained by a similar procedure to that described in the preceding Example, starting with 3-(3-nitrobenzamido)propionitrile, m.p. 104—105°C., forming successively:

3-(3-nitrobenzamido)propionamidine hydrochloride, m.p. 210—212°C.;

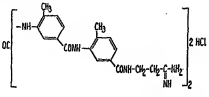
3-(3-aminobenzamido)propionamidine hydrochloride, m.p. 194—196°C.;

3-[3-(3-nitro-4-methylbenzamido)benzamido]propionamidine hydrochloride, m.p. 140—143°C., and

3-[3-(3-amino-4-methylbenzamido)benzamido]propionamidine hydrochloride, m.p. 213—214°C.

EXAMPLE VI

By the procedure indicated in the foregoing Examples and starting with 3-[3-(3-amino-4-methylbenzamido)-4-methylbenzamido]propionamidine hydrochloride (3.9 g., 0.01 mol.) and carbonyldiimidazole (1.35 g.) there is obtained a product (1.4 g.), m.p. 210—215°C., of the formula:



The amidino starting material is obtained by a procedure similar to that described in Example IV, starting with 3-(3-nitro-4-methylbenzamido)propionitrile, m.p. 141°C., there being successively formed:

3-(3-nitro-4-methylbenzamido)propionamidine hydrochloride, m.p. 228—230°C.;

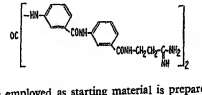
3-(3-amino-4-methylbenzamido)propionamidine hydrochloride, m.p. 225—228°C.;

3 - [3 - (3 - nitro - 4 - methylbenzamido) - 4 - methylbenzamido] propionamidine hydrochloride, m.p. 130—131°C., and

3 - [3 - (3 - amino - 4 - methylbenzamido) - 4 - methylbenzamido] propionamidine hydrochloride, m.p. 231—232°C.

EXAMPLE VII

To a suspension of 3-(3-aminobenzamido)propionamidine hydrochloride (1.65 g.) in dimethylformamide (8 cc.) are added a solution of 1,3-bis(3-chlorocarbonylphenyl)-urea in dimethylformamide (8 cc.), [prepared as indicated hereinafter], and pyridine (1.5 cc.). The mixture is heated at 80—85°C. for 1 hour 30 min., and the dimethylformamide is then eliminated under reduced pressure. There remains an oily product which is triturated in the presence of acetone (4 × 50 cc.) and then redissolved in water (100 cc.). To the aqueous solution thus obtained is added sodium fumarate (0.7 g.) in solution in a minimum quantity of water. The precipitate which forms is filtered off, washed and dried at 100°C. *in vacuo*, and is the fumarate of the base of the formula:



The acid chloride employed as starting material is prepared as follows:

Two mols. of 3-aminobenzoic acid and 1 mol. of urea are heated together overnight at 150—160°C. and then at 180°C. for 2 hours to form 1,3-bis(3-carboxyphenyl)urea, m.p. 280—290°C.

Thionyl chloride (1 cc. in solution in 3 cc. of dimethylformamide) is reacted with the aforesaid diacid (2.2 g.) in solution in dimethylformamide (8 cc.), the temperature being maintained at 30°C. overnight. The dissolved gases (SO_2, HCl) are then eliminated and the volume adjusted to 13 cc. by addition of dimethylformamide to yield a solution of 1,3-bis(3-chlorocarbonylphenyl)urea in that amide.

The present invention includes within its scope pharmaceutical compositions which comprise at least one of the compounds of general formula I, or a non-toxic acid addition salt thereof, in association with a pharmaceutically-acceptable carrier or coating. In clinical practice the compounds of the present invention will normally be administered parenterally.

Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or suspending media are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. These compositions may also contain

adjuvants such as preserving, wetting, emulsifying and dispersing agents. They may be sterilised by, for example, filtration through a bacteria-retaining filter, by incorporation in the compositions of sterilising agents, by irradiation, or by heating. They may also be manufactured in the form of sterile solid compositions, which can be dissolved or dispersed in sterile water or some other sterile injectable medium immediately before use.

Solid compositions for oral administration include compressed tablets, pills, powders, and granules. In such solid compositions one or both of the active compounds is, or are, admixed with at least one inert diluent such as starch, sucrose or lactose. The compositions may also comprise, as is normal practice, additional substances other than inert diluents, e.g. lubricating agents, such as magnesium stearate. Liquid compositions for oral administration include pharmaceutically-acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art, such as water and liquid paraffin. Besides inert diluents such compositions may also comprise adjuvants, such as wetting and suspending agents, and sweetening, flavouring, perfuming and preserving agents. The compositions according to the invention, for oral administration, also include capsules of absorbable material such as gelatin containing one or more of the active substances with or without the addition of diluents or excipients.

The percentage of active ingredient in the compositions of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. The dosage will depend upon the therapeutic effect sought, the route of administration and the length of treatment. In human therapy the compositions should generally be administered so as to give to an adult, in the case of intramuscular or subcutaneous administration, between 50 and 200 mg. of active substance per day.

The following Examples illustrate pharmaceutical compositions according to the invention.

EXAMPLE VIII

Extemporaneous suspension for injection.

There is aseptically distributed in ampoules:

product of Example 1 (hydrated fumarate) finely divided ... 65.9 mg. per ampoule.

At the time of use, the contents of one ampoule are suspended in 1 cc. of physiological serum.

EXAMPLE IX

Extemporaneous suspension for injection.

There is aseptically distributed in ampoules:

product of Example 2, finely divided ..... 55.4 mg. per ampoule.

At the time of use, the contents of one ampoule are suspended in 1 cc. of physiological serum.

EXAMPLE X

Extemporaneous suspension for injection.

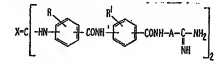
There is aseptically distributed in ampoules:

product of Example 3, finely divided ..... 55.4 mg. per ampoule.

At the time of use, the contents of one ampoule are suspended in 1 cc. of physiological serum.

WHAT WE CLAIM IS:—

1. Urea and thiourea derivatives of the general formula:



wherein X represents an oxygen or sulphur atom, A represents a straight or branched alkylene group having from 1 to 4 carbon atoms, the groupings NH and CO attached to a common benzene nucleus are in *meta*- or *para*-position in relation to one another, each of the symbols R and R', which are identical or different, represents a hydrogen atom or a methyl group, and the groupings NH and CH_2 attached to a common benzene nucleus are in *ortho*-position in relation to one another, and acid addition salts thereof.

2. Urea compounds according to claim 1 wherein X represents an oxygen atom, the groupings NH and CO attached to a common benzene nucleus are in *meta*-position in relation to one another, and R and R' represent hydrogen atoms.

3. Urea and thiourea compounds according to claim 1 wherein R and R′ represent hydrogen atoms.

4. Urea and thiourea compounds according to claim 1 wherein one of the symbols R and R′ represents a methyl group and the other represents a hydrogen atom or a methyl group.

5. Urea and thiourea compounds according to any one of the preceding claims in which A is ethylene.

6. 1,3 - Bis - {3 - [3 - (2 - amidinoethyl)carbamoylphenyl] carbamoylphenyl} - urea, and acid addition salts thereof.

7. 1,3 - Bis{3 - [3 - (2 - amidinoethyl)carbamoyl - 6 - methylphenyl] carbamoyl-phenyl}urea, and acid addition salts thereof.

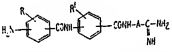
8. 1,3 - Bis{3 - [3 - (2 - amidinoethyl)carbamoylphenyl] carbamoyl - 6 - methyl-phenyl}urea, and acid addition salts thereof.

9. 1,3 - Bis{3 - [3 - (2 - amidinoethyl)carbamoyl - 6 - methylphenyl] carbamoyl-6-methylphenyl}urea, and acid addition salts thereof.

10. 1,3 - Bis{4 - [4 - (2 - amidinoethyl)carbamoylphenyl] carbamoylphenyl} - urea, and acid addition salts thereof.

11. 1,3 - Bis{4 - [4 - (2 - amidinoethyl)carbamoylphenyl] carbamoylphenyl} - thiourea, and acid addition salts thereof.

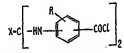
12. Process for the preparation of urea and thiourea compounds as claimed in claim 1 which comprises reacting two moles of an amino-amidine of the general formula:



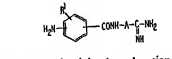
(wherein the symbols are as defined in claim 1 and in which the position of the substituents is that indicated in claim 1), or an acid addition salt thereof, with one mole of carbonyldiimidazole or thiocarbonyldiimidazole with or without an inert and anhydrous organic solvent at a temperature between ambient temperature and 120°C., and optionally converting the product obtained into an acid addition salt.

13. Process according to claim 12 wherein the amino-amidine reactant is in the form of the hydrochloride and the reaction is effected in solution in anhydrous dimethylformamide at a temperature between 20° and 85°C.

14. Process for the preparation of urea and thiourea compounds as claimed in claim 1 which comprises reacting one mole of a dichloride of the formula:



with two moles of an amino-amidine of the general formula:



wherein X, R and R′ are as defined in claim 1, and optionally converting the product obtained into an acid addition salt.

15. Process for the preparation of urea compounds as claimed in claim 1 substantially as described in Example I.

16. Process for the preparation of urea and thiourea compounds as claimed in claim 1 substantially as described in Example II or III.

17. Process for the preparation of urea and thiourea compounds as claimed in claim 1 substantially as described in Example IV, V or VI.

18. Process for the preparation of urea and thiourea compounds as claimed in claim 1 substantially as described in Example VII.

19. Urea and thiourea derivatives of the formula specified in claim 1, and acid addition salts thereof, when prepared by the process claimed in any one of claims 12 to 18.

20. Pharmaceutical compositions which comprise at least one urea or thiourea

derivative as claimed in any one of claims 1 to 11 and 19, or a non-toxic acid addition salt thereof, in association with a pharmaceutically acceptable carrier or coating.

21. Pharmaceutical compositions according to claim 20 substantially as hereinbefore described with especial reference to Example VIII, IX or X.

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